Development of a 24-Hour Air Monitoring Comparison Value (AMCV) for 1,3-Butadiene and Comparison of 1-Hour, 24-Hour and Chronic AMCVs to Observed Adverse Effect Levels

R.L. Grant and R.E. Jones, Texas Commission on Environmental Quality (TCEQ), Austin, TX

Abstract # 2223
Poster Board # 421

Scan Me! Access an electronic version of this poster.

Abstract

The TCEQ develops AMCVs, which are considered safe concentrations of chemicals in air, to determine whether 1-hour (hr) or annual average chemical concentrations in ambient air exceed levels of potential concern for adverse health effects. Previously for 1,3-butadiene (BD), a 1-hr AMCV of 1,700 ppb was derived based on a mouse developmental study (6 hr/day exposures, gestational days 6-15). A chronic AMCV of 9.1 ppb was derived based on a 1 in 100,000 excess risk for leukemia mortality from an epidemiological study in styrene-butadiene workers. To calculate annual ambient air concentrations, the TCEQ collects a significant amount of 24-hr monitoring data that are not directly comparable to the 1-hr or chronic AMCV. Therefore, the TCEQ has developed a 24-hr AMCV for BD to evaluate the potential for health effects from 24-hr exposure. The same mouse study used for the 1-hr AMCV was judged to be the critical study for the 24-hr AMCV based on mode-of-action and toxicokinetic data. The 6-hr human equivalent point of departure (POD-HEC) of 51,300 ppb was duration adjusted (Haber's rule with n = 1) to calculate the 24-hr POD-HEC of 12,800 ppb. The proposed 24-hr AMCV is 430 ppb after application of total uncertainty factors of 30. The TCEQ has developed guidelines to derive observed adverse effects levels (OAELs) based on available dose-response data to better communicate to risk managers and the public the margin of safety between OAELs and AMCVs. For the 1-hr AMCV, the acute OAEL is 66,000 ppb (the central estimate POD-HEC for 5% decrease in fetal weight loss). The 1-hr AMCV of 1700 ppb is 39 times lower than the acute OAEL. The chronic OAEL is 10,000 ppb (the lowest average occupational exposure concentration where the likelihood ratio test that slope = 0 was statistically significant for different maximum levels of cumulative BD ppm-years for leukemia deaths). The chronic AMCV of 9.1 ppb is 1,100 times lower than the chronic OAEL.

Introduction

A 24-hr Reference Value, used as an AMCV, is derived for human health hazards associated with threshold dose-response relationships (typically effects other than cancer) and is defined as an estimate of an inhalation exposure concentration that is likely to be without an appreciable risk of adverse effects to the human population (including susceptible subgroups) for a 24-hr exposure.

The critical step in deciding whether or not to derive a 24-hr ReV is the availability of appropriate toxicity studies that provide meaningful information to evaluate a 24-hr exposure duration. An evaluation of the mode of action, dose metric, and the toxicokinetics and toxicodynamics of the chemical of concern as well as exposure duration adjustments that are unique for the derivation of a 24-hr ReV is conducted. The same analytical steps used to derive acute 1-hr ReVs and chronic ReVs (TCEQ 2012) are used to derive a 24-hr ReV. OECD (2010) also provides guidance applicable to the development of acute reference concentrations.

Key Studies

BD has very low acute toxicity (TCEQ 2008). Figure 1 is an exposure response array for acute (less than 24-hr) and subacute studies which were considered for the development of a 24-hr ReV.

Critical Study

The TCEQ developed a 1-hr ReV in 2008 (TCEQ 2008) based on developmental toxicity in mice, the most sensitive species, after BD exposure (Hackett *et al.* 1987b). This study was also selected for development of the 24-hr ReV, based on toxicokinetic and mode of action analysis. In addition, reproductive and developmental effects may have been caused by only a single day's exposure that occurred at a critical time during gestation. Therefore, this developmental study is relevant for derivation of a 24-hr ReV; this acute study has the lowest LOAEL and NOAEL (Figure 1).

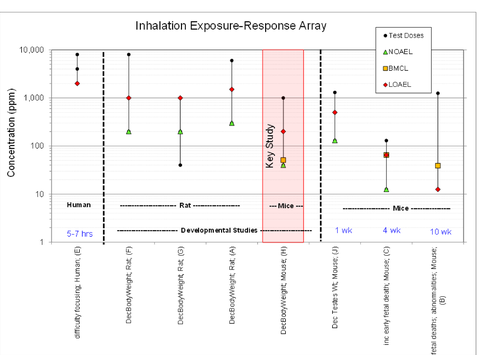

Figure 1. BD Exposure response array for acute (less than 24-hr) and subacute studies

Citation	Key	Citation	Key	Citation	Key
ACC (2003)	A	Carpenter *et al.* (1944)	E	Hackett *et al.* (1987b)	H
Anderson *et al.* (1996)	B	IISRP (1982)	F	Pacchierotti *et al.* (1998)	J
Anderson *et al.* (1998)	C	Hackett *et al.* (1987a)	G		

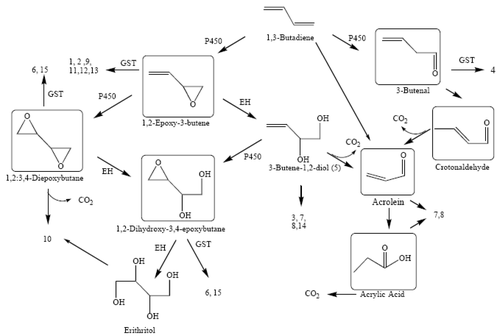

Figure 2: Schematic of BD metabolism (Figure 3-1 from USEPA [2002]) P450 stands for cytochrome P450, EH stands for epoxide hydrolase, GST stands for glutathione transferase, and GSH stands for glutathione. The reactive metabolites are shown inside boxes. The urinary metabolites are numbered and listed in Table 3-1 of USEPA (2002).

Toxicokinetics and Mode of Action

BD is a highly volatile, colorless gas with a mildly aromatic odor, and is only slightly soluble in water. Absorption through the lung is limited by blood flow to the lung. After absorption, BD is distributed throughout the body. For both rats and mice after exposure to ^{14}C-butadiene, Bond *et al.* (1987) reported the following:

- Within 1 hr after the end of exposure, respiratory tissue, gastrointestinal tract, liver, kidneys, urinary bladder and pancreas contained higher concentrations of radioactivity than other tissues and
- Elimination of BD from tissues and blood was rapid, with 77% to 99% of the initial tissue burden being eliminated with half-times of 2 to 10 hr.

Research has shown that BD produces toxicity when metabolized to reactive metabolites. 1,2-Epoxy-3-butene (EB) and 1,2;3,4-diepoxybutane (DEB) are the two metabolites that are most reactive, after animals are exposed to BD (Figure 2).

There is a difference in the metabolism between mice and rats that is related to the greater production of toxic intermediates and a lower capacity for detoxification of these intermediates in mice compared to rats (USEPA 2002). Humans are more similar to rats in the metabolism of BD. Humans produce much lower levels of DEB than mice as demonstrated by experimental data on DEB-specific pyr-Val Hb adducts (Swenberg *et al.* (2007); Georgieva *et al.* (2007; 2008) and urinary metabolites (Sabourin *et al.* 1992).

The specific mechanism of action for the maternal reproductive/developmental effects produced by BD is unknown after acute exposure, although the mode of action (MOA) may involve DEB-induced ovarian atrophy and a decrease in serum progesterone levels (Spencer *et al.* (2001) and Chi *et al.* (2002)). Although the amount of DEB produced by humans is much lower than mice, reproductive/developmental effects were assumed to be relevant to humans (Kirman and Grant 2012).

Based on toxicokinetic and MOA information, the reproductive/developmental effects in mice are considered to have a threshold and to be concentration and duration dependent.

Table 1 compares the derivation of the 24-hr ReV to the derivation of the 1-hr ReV and a 24-hr ReV value based on a rat study (ACC 2003).

Table 1: Derivation of the 1-hr Acute ReV and 24-hr ReV			Alternate Derivation in Rats
Study	Hackett *et al.* 1987b		ACC 2003
Study population	CD-1 mice (18-21 pregnant mice per dose group)		Crl:CD® (Sprague-Dawley) IGS BR rats (12 male and 12 female rats per dose group)
Study quality	High		High
Exposure Methods	0, 40, 200, and 1,000 ppm on gestation days (GD) 6-15 for 6 hr/day		0, 300, 1,500, and 6,000 ppm (14 days prior to breeding, during gestation, and lactation) for 6 hr/day
Critical Effects	Reduction in extragestational weight gain and fetal body weight; developmental toxicity		Persistent reductions in body weight parameters in F_0 and F_1 males and females
	6-hr Acute ReV mice	**24-hr Acute ReV mice**	**24-hr Acute ReV rat**
POD	51.3 ppm ($BMCL_{1\ SD}$)	51.3 ppm ($BMCL_{1\ SD}$)	300 ppm (NOAEL)
Duration	6 hr	6 hr	6 hr
Extrapolation to other durations	No adjustment to 1 hr because the critical effect was a maternal/ developmental endpoint	Extrapolation to 24 hr 51.3 ppm ($BMCL_{1\ SD}$) x 6/24	Extrapolation to 24 hr 300 ppm (NOAEL) x 6/24
POD_{animal}	6-hr POD_{mice} = 51.3 ppm ($BMCL_{1\ SD}$)	24-hr POD_{mice} = 12.8 ppm ($BMCL_{1\ SD}$)	24-hr POD_{rat} 75 ppm (NOAEL)
POD_{HEC}	6-hr POD_{HEC} 51.3 ppm (gas with systemic effects, based on default RGDR = 1.0)	24-hr POD_{HEC} 12.8 ppm (gas with systemic effects, based on default RGDR = 1.0)	24-hr POD_{HEC} 75 ppm (gas with systemic effects, based on default RGDR = 1.0)
Total uncertainty factors (UFs)	30	30	30
Interspecies UF	3	3	3
Intraspecies UF	10	10	10
LOAEL UF	Not applicable	Not applicable	Not applicable
Database UF	1	1	1
Database Quality	High	High	High
acute ReV	**3,700 µg/m³ (1,700 ppb) [1 hr] mice**	**950 µg/m³ (430 ppb) [24 hr] mice**	**5,500 µg/m³ (2,500 ppb) [24 hr] rat**

Dose Metric, Dose-Response Modeling, and Points of Departure (PODs)

Data on the exposure concentration of the parent chemical was used as the default dose metric since more appropriate dose metrics were not available The TCEQ (2008) performed benchmark concentration (BMC) modeling for numerous endpoints from Hackett *et al.* (1987b). The endpoint with the lowest relevant BMCL was decrease in maternal extragestational weight gain ($BMCL_{1\ SD}$ = 51.3 ppm with a $BMC_{1\ SD}$ of 723 ppm), followed by decrease in fetal body weight ($BMCL_{05}$ = 54.7 ppm BMC_{05} of 65.8 ppm).

Duration and Default Dosimetry Adjustments

Table 1 provides information on duration adjustments from a 6-hr exposure to a 24-hr exposure using Haber's Rule as modified by ten Berge (1986) with "n" = 1. Default dosimetry adjustments from animal-to-human exposure were based on methods for Category 3 gases producing systemic effects (USEPA 1994; TCEQ 2012).

Uncertainty Factors

A full intrahuman UF (UF_H) of 10 was used to account for intraspecies variability. There is experimental evidence that indicates BD-sensitive human subpopulations may exist due to metabolic genetic polymorphisms (USEPA 2002), although recent studies indicate that variability due to genetic polymorphisms is less than 10 based on metabolism of BD in humans with different genotypes. (Albertini *et al.* 2001, 2003).

An animal to human UF (UF_A) of 3 was used for extrapolation from animals to humans because toxicokinetic adjustments were made but not toxicodynamic differences.

A database UF (UF_D) of 1 was used because the overall acute toxicological database for BD includes acute inhalation studies in humans; two inhalation bioassays in different species investigating a wide range of endpoints; and several prenatal developmental toxicity studies in different species (USEPA 2002; TCEQ 2008). Both the quality of the studies and the confidence in the acute database is high.

Health-Based Acute ReVs

The 24-hr ReV for BD is 430 ppb (950 µg/m^3), whereas the 1-hr acute ReV is 1,700 ppb (3,700 µg/m^3) (TCEQ 2008). These acute ReVs are considered to be conservative since pregnant mice exposed to BD and their offspring develop maternal/developmental toxicity much easier than similarly-exposed rats, available scientific information suggests mice are more sensitive than humans, and BD-induced reproductive/ developmental effects have never been observed in humans (TCEQ 2008).

Table 1 shows that if the highest quality rat study was used (ACC 2003), the 24-hr ReV would be 2,500 ppb (5,500 µg/m^3); this value is more applicable to humans.

Figure 3 shows a comparison of the 1-hr, 24-hr and chronic AMCVs.

Observed Adverse Effect Levels (OAELs)

OAELs are air concentrations where health effects would be expected to occur (TCEQ 2012). More specifically, an $LOAEL_{HEC}$ determined from human studies, where effects occurred in some individuals, represents a concentration at which similar effects probably could occur in some individuals exposed to this level over the same duration as used in the study or longer. UFs and duration adjustments not based on a PBPK or other optimal inhalation models are not made to derive OAELs. If an animal LOAEL is used, then predictive animal-to-human dosimetric adjustments are conducted to derive $LOAEL_{HEC}$. OAELs are derived to better communicate to risk managers and the public the margin of safety between OAELs and AMCVs (TCEQ 2012).

Acute OAELs

For the 1-hr AMCV, the acute OAEL is 66,000 ppb (the central estimate POD_{HEC} for 5% decrease in fetal weight loss observed by Hackett *et al.* (1987b) (Figure 3). The value is based on the HEC BMC_{05} of 65.8 ppm (note: the HEC $BMC_{1\ SD}$ for reduction in extragestational weight gain was 723 ppm). Although the 24-hr AMCV is based on the Hackett *et al.* (1987b) study, there isn't reliable, predictive data to derive a meaningful 24-hr OAEL. The 1-hr AMCV of 1700 ppb is 39 times lower than the acute OAEL. For comparison, the 50% odor-detection threshold is 230 ppb (Nagata 2003).

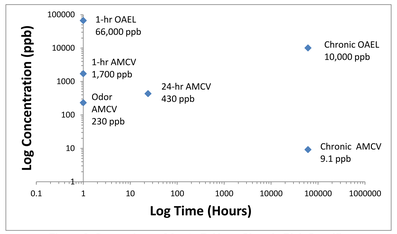

Figure 3. Comparison of Acute ReVs or Chronic Risk-Specific Concentrations to OAELs

Chronic OAELs

For determination of chronic OAELs, data from Table 2 of Sielken *et al.* (2011) were used. The chronic OAEL is 10,000 ppb (the lowest average occupational exposure concentration where the likelihood ratio test that slope = 0 was statistically significant for different maximum levels of cumulative BD ppm-years for leukemia deaths in a cohort epidemiology study of styrene-butadiene occupational workers) (Sielken *et al.* 2011). The chronic AMCV of 9.1 ppb is 1 in 100,000 excess risk for leukemia mortality (TCEQ 2008). The chronic AMCV of 9.1 ppb is 1,100 times lower than the chronic OAEL (Figure 3).

Ambient Air Monitoring Data from 24-Hr Canister Samplers from 2010-2011

Figure 4 shows 2010-2011 ambient air monitoring data for BD from 24-hr VOC canister samples at monitoring sites with the highest annual averages across the state (Port Neches > Groves > Galena Park > Jacinto Port > Jefferson County Airport) (5 out of a total of 47 sites 24-hr canister VOC samplers). The detected 24-hr BD peak values were below the chronic AMCV of 9.1 ppb. Based on almost 5,500 samples taken over 2010 and 2011 throughout Texas, the annual average BD was 0.25 ppb.

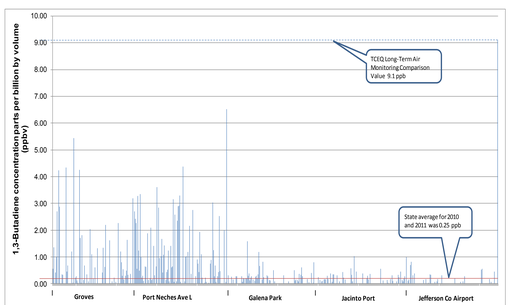

Figure 4 Top five sites with the highest 1,3-butadiene annual average concentrations (01/01/2010 - 12/31/2011)

Conclusions

- The 24-hr, health-based AMCV for 1,3-butadiene is 950 µg/m^3 (430 ppb) based on mice reproductive/developmental effects.
- This 24-hr AMCV falls between the TCEQ acute 1-hr AMCV of 1,700 ppb and the carcinogenic-based chronic AMCV of 9.1 ppb.
- The 24-hr value is sufficiently conservative for the adequate protection of public health for the exposure duration and adverse effects considered and significantly complements TCEQ health-effect evaluations of ambient air data, which currently utilize 1-hr and chronic (i.e., lifetime) health-protective and welfare-based (i.e., odor, vegetation) AMCVs.
- BD ambient air monitoring data from 24-hr canister samples (2010-2011) are well below the 24-hr AMCV of 430 ppb and the chronic AMCV of 9.1 ppb.

References

Albertini, RJ, RJ Sram, PM Vacek, *et al.* 2001. Biomarkers for assessing occupational exposures to 1,3-butadiene. *Chem Biol Interact* 135-136: 429-53.
Albertini, RJ, RJ Sram, PM Vacek, *et al.* 2003. Biomarkers in Czech workers exposed to 1,3-butadiene: A translational epidemiological study. HEI Research Report 116.
American Chemistry Council (ACC). 2003. An inhalation reproduction/developmental toxicity screening study of 1,3-butadiene in rats. Wil. Research Laboratories. OLF-88.0-BD-HPV-WIL.
Anderson, D, JA Hughes, AJ Edwards, and MH Brinkworth. 1996. Male-mediated F1 effects in mice exposed to 1,3-butadiene. *Toxicology* 113: 128-37.
Anderson, D, JA Hughes, AJ Edwards, and MH Brinkworth. 1998. A comparison of male-mediated effects in rats and mice exposed to 1,3-butadiene. *Mutat Res* 397: 77-84.
Carpenter, CP, CB Shaffer, CSWeil, and HF Smyth, Jr. 1944. Studies on the inhalation of 1,3-butadiene, with a comparison of its narcotic effect with benzol, toluol, and styrene, and a note on the elimination of styrene by the human. *J Ind Hyg Toxicol* 26: 69-78.
Chi, L, E Nixon, and F Spencer. 2002. Uterine-ovarian biochemical and developmental interactions to the postimplantation treatment with 1,2-epoxybutene and 1,2:3,4-diepoxybutane in female Sprague-Dawley rats. *Toxicol Sci* 67: 153-163.
Georgieva, NL, G Bowen, P Upton, *et al.* 2007. Analysis of 1,2:3, 4-diepoxybutane specific protein adduct in occupationally exposed workers. *The Toxicologist Abstract* #428: 89.
Georgieva, NL, G Bowen, P Upton, *et al.* 2008. Analysis of 1,2:3, 4-diepoxybutane specific protein adduct in occupationally exposed workers, Part 2. *The Toxicologist Abstract* #1736: 356-7.
Gross, SA, GM Ginsberg, BL Finley, and DJ Paustenbach. 2002. Spatial and temporal trend evaluation of ambient concentrations of 1,3-butadiene and chloroprene in Texas. *Chem Biol Inter* 166: 44-51.
Hackett, PL, MR Sikov, TJ Mast, *et al.* 1987a. Inhalation developmental toxicology studies of 1,3-butadiene in the rat (final report). Richland, W A.: Pacific Northwest Laboratory; PNL Report No. PNL-6414 UC-48; NIH Report No. NIH- 401-ES-4-0231-101 p. Prepared for NIEHS, NTP, under a Related Services Agreement with the U.S. Department of Energy under contract DE-AC06-76RLO 1830.
Hackett, PL, MR Sikov, TJ Mast, *et al.* 1987b. Inhalation developmental toxicology studies. Teratology study of 1,3-butadiene in mice (final report). Richland, W A.: Pacific Northwest Laboratory; PNL Report No. PNL-6412 UC-48; NIH Report No. NIH- 401-ES-4-0231-101 p. Prepared for NIEHS, NTP, under a Related Services Agreement with the U.S. Department of Energy under contract DE-AC06-76RLO 1830.
International Institute of Synthetic Rubber Producers (IISRP). 1982. 1,3-Butadiene: Inhalation teratogenicity in the rat (final report with cover letter dated 08/11/82). Report no. 2798-5223; submission IEH02-0382-0441. Hanwarden, England: Hazleton Laboratories Europe, Ltd.
Kirman, CR, and RL Grant. 2012. Quantitative human health risk assessment for 1,3-butadiene based upon ovarian effects in rodents. *Reg. Tox. Pharm.* 62: 371-384.
Nagata, Y. 2003. Measurement of odor threshold by triangular odor bag method. Odor Measurement Review, Japan Ministry of the Environment, pp. 118-127.
Organisation for Economic Co-operation and Development (OECD) 2010. Draft OECD Guidance document for the derivation of an Acute Reference Concentration. ENV/JM/MONO(2010)18.
Pacchierotti, F, C Tiveron, R Ranaldi, *et al.* 1998. Reproductive toxicity of 1,3-butadiene in the mouse: Cytogenetic analysis of chromosome aberrations in first-cleavage embryos and flow cytometric evaluation of spermatogonial cell killing. *Mutat Res* 397: 85-94.
Sielken, RL and E Valdez-Flores. 2011. Butadiene cancer exposure-response modeling: Based on workers in the styrene-butadiene rubber industry. Total cohort and mortality for myelogenous leukemia, chronic lymphocytic leukemia, and chronic myelogenous leukemia. *Reg Tox Pharm* 60: 332-41.
Spencer, F, L Chi, and M Zhu. 2001. A mechanistic assessment of 1,3-butadiene diepoxide-induced inhibition of uterine deciduoma formation in female Sprague-Dawley rats. *Toxicol Sci* 63: 189-197.
Swenberg, JA, G Bowen, N Georgieva, *et al.* 2007. Future directions in butadiene risk assessment and the role of cross-species internal dosimetry. *Chem Biol Inter* 166: 78-93.
ten Berge, WF, A Zwart, LM Appelman. 1986. Concentration-time mortality response relationship of irritant and systemically acting vapours and gases. *J Hazard Mater* 13: 301-09.
Texas Commission on Environmental Quality (TCEQ). 2012. TCEQ Guidelines to Develop Toxicity Factors. Office of the Executive Director, RG-442, revised.
Texas Commission on Environmental Quality (TCEQ). 2008. Development Support Document 1,3-Butadiene CAS Registry Number: 106-99-0. Austin, TX. Available at: http://www.tceq.texas.gov/toxicology/dsd/final.html
United States Environmental Protection Agency (USEPA). 1994. Methods for derivation of inhalation reference concentrations and application of inhalation dosimetry. Environmental Criteria and Assessment Office, Office of Research and Development, Washington D.C.
United States Environmental Protection Agency (USEPA). 2002. Health Assessment of 1,3-Butadiene. EPA/600/P-98/001F, National Center for Environmental Assessment, Office of Research and Development, Washington D.C.